Docket No.: PF-0041-4 CON

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#7
B.G.
12/4/02

In re Application of: Coleman et al.

Title: POLYNUCLEOTIDES ENCODING THROMBIN RECEPTOR HOMOLOGS

Serial No.: 09/997,522 Filing Date: November 28, 2001

Examiner: Landsman, R.S. Group Art Unit: 1647

Box Non-Fee Amendment
Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF LARS MICHAEL FURNESS UNDER 37 C.F.R. § 1.132

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, Western and Northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In 1998, I moved to Incyte to work in the Pharmacogenomics group, looking at the application of genomics and proteomics to the pharmaceutical industry. In 1999, I was appointed Director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001, I founded Nuomics Consulting, Ltd., in Exning, UK, where I am currently employed as Managing Director. Nuomics Consulting, Ltd. provides expert technical knowledge and advice to businesses in the areas of genomics, proteomics, pharmacogenomics, toxicogenomics, and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on November 28, 2001 in the names of Roger Coleman et al. and was assigned Serial No. 09/997,522 (hereinafter "the Coleman '522 application"). Furthermore, I understand that this United States patent application was a continuation application of, and claimed priority to, United States patent application Serial No. 09/643,383, filed on August 21,

2000 (hereinafter "the Coleman '383 application"), which was a divisional application of, and claimed priority to, United States patent application Serial No. 09/217,101, filed on December 21, 1998 (hereinafter "the Coleman '101 application"), which was a divisional application of, and claimed priority to, United States patent application Serial No. 08/911,320, filed on August 14, 1997 (hereinafter "the Coleman '320 application"), which was a divisional application of, and claimed priority to, United States patent application Serial No. 08/467,125, filed on June 6, 1995 (hereinafter "the Coleman '125 application"). The Coleman '522, Coleman '383, Coleman '101, Coleman '320, and Coleman '125 applications were filed with essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the Coleman '522, Coleman '383, Coleman '101, Coleman '320, and Coleman '125 applications. My remarks herein will therefore be directed to the Coleman '125 patent application, and June 6, 1995, as the relevant date of filing. In broad overview, the Coleman '125 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of immune disorders and trauma), and (b) monitoring the activity of drugs for purposes related to evaluating their efficacy and toxicity.

4. I understand that (a) the Coleman '522 application contains claims that are directed to isolated polynucleotides which encode a polypeptide having the sequence shown as SEQ ID NO:2, for example SEQ ID NO:1 (hereinafter "the SEQ ID NO:2-encoding polynucleotides"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Coleman '522 application does not disclose a specific, substantial, and credible asserted utility or a well established utility for polypeptides having the sequence shown as SEQ ID NO:2 (hereinafter "the SEQ ID NO:2 polypeptide"), or for the SEQ ID NO:2-encoding polynucleotides. I further understand that whether or not a patent specification discloses a specific, substantial, and credible asserted utility or a well established utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time the patent application was filed. In addition, I understand that a specific, substantial, and credible asserted utility or a well established utility under the

patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Coleman '522 application and its parents, the Coleman '383, Coleman '101, Coleman '320, and Coleman '125 applications, do not disclose a specific, substantial, and credible "real-world" utility for the SEQ ID NO:2 polypeptide or, by extension, for the SEQ ID NO:2-encoding polynucleotides, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Coleman '125 application pertains on June 6, 1995, would have concluded that the Coleman '125 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:2 polypeptide and, by extension, the SEQ ID NO:2-encoding polynucleotides, in their then available and disclosed forms. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

> "Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Coleman '125 patent application disclosed to a person skilled in the art at the time of its filing a number of specific, substantial, and credible real-world utilities for the SEQ ID NO:2 polypeptide and, by extension, the SEQ ID NO:2-encoding polynucleotides. More specifically, persons skilled in the art on June 6, 1995, would have understood the Coleman '125 application to disclose the use of the SEQ ID NO:2 polypeptide as a research tool in a number of gene and protein expression monitoring applications that were well-known at that time to be

useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Coleman '125 application, and (b) a number of published articles that evidence gene and protein expression monitoring techniques that were well-known before the June 6, 1995 filing date of the Coleman '125 application. The published articles I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S., Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1991 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphrey-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimentional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the

Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F);

(g) Large Scale Biology Company Info; LSB and LSP Information; from http://www.lsbc.com (2001) (copy annexed at Tab G);

(h) Stadel, J.M., Wilson, S., Bergsma, D.J., Orphan G Protein-coupled Receptors: A Neglected Opportunity for Pioneer Drug Discovery, Trends in Pharmacological Sciences, 18, 430-437 (1997) (hereinafter "the Stadel review") (copy annexed at Tab H); and

(i) Wilcox, J.N., Rodriguez, J., Subramanian, R., Ollerenshaw, J., Zhong, C., Hayzer, D.J., Horaist, C., Hanson, S.R., Lumsden, A., Salam, T.A., Kelly, A.B., Harker, L.A., Runge, M., Characterization of Thrombin Receptor Expression During Vascular Lesion Formation, Circulation Research, 75, 1029-1038 (1994) (hereinafter "the Wilcox article") (copy annexed at Tab I).

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in gene and protein expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Coleman '125 application on June 6, 1995 would have understood that application to disclose the SEQ ID NO:2 polypeptide, and by extension the SEQ ID NO:2-encoding polynucleotides, to be useful for a number of gene and protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

9. Turning more specifically to the Coleman '125 specification, the SEQ ID NO:2 polypeptide is shown at pages 28-31 as one of two sequences under the heading "Sequence Listing." The Coleman '125 specification specifically teaches that the "invention provides a unique nucleotide sequence identifying a novel homolog of thrombin receptor . . . The sequence

for TRH is shown in SEQ ID No 1" (Coleman '125 application at page 7, lines 12-14). It further teaches that (a) the identity of the SEQ ID NO:1 polynucleotide was determined from "the cDNAs of a liver library," (b) the SEQ ID NO:1 polynucleotide encodes the thrombin receptor homolog shown as SEQ ID NO:2 and referred to as "TRH," (c) "an assay for upregulated expression of TRH can accelerate diagnosis and proper treatment of conditions caused by abnormal signal transduction due to systemic and local infections, traumatic and other tissue damage, hereditary or environmental diseases associated with hypertension, carcinomas, and other pathologic problems," and (d) "[s]ince TRH was found in a human liver library, it appears to be upregulated in cell types mainly involved in immune protection or defense" (Coleman '125 application at page 5, lines 2-5; page 7, lines 12-22; page 22, lines 9-11; and Figures 1A and 1B).

The Coleman '125 application discusses a number of uses of the SEQ ID NO:2 polypeptide and the SEQ ID NO:2-encoding polynucleotides, in addition to their use in gene and protein expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Coleman '125 specification discloses these additional uses to be specific, substantial, and credible real-world utilities of the SEQ ID NO:2 polypeptide. Consequently, my discussion in this Declaration concerning the Coleman '125 application focuses on the portions of the application that relate to the use of the SEQ ID NO:2 polypeptide, and the SEQ ID NO:2-encoding polynucleotides, in gene and protein expression monitoring applications.

10. The Coleman '125 application discloses that the SEQ ID NO:2 polypeptide is useful in protein expression detection technologies. The Coleman '125 application states that "[a] variety of protocols for measuring soluble or membrane-bound TRH, using either polyclonal or monoclonal antibodies specific for the protein, are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and fluorescent activated cell sorting (FACS)" (Coleman '125 application at page 22, lines 23-26). Furthermore, the Coleman '125 application discloses that "[p]articular TRH antibodies are useful for investigating signal transduction and the diagnosis of infectious or hereditary conditions which are characterized by differences in the amount or distribution of TRH or downstream products of

an active signalling cascade. . . Diagnostic tests for TRH include methods utilizing antibody and a label to detect TRH in human body fluids, membranes, cells, tissues or extracts of such (Coleman '125 application at page 22, lines 7-13).

In addition, at the time of filing of the Coleman '125 application, it was well known in the art that "gene" and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length, and how that standard curve can be used in protein expression analysis (Tab A at p. 911). The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at p. 912).

The Wilkins article is one of a number of documents that were published shortly after the June 6, 1995 filing date of the Coleman '125 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Coleman '125 application, the Wilkins article, and other related pre- and post-June 1995 publications, persons skilled in the art on June 6, 1995 clearly would have understood the Coleman '125 application to disclose the SEQ ID NO:2 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and for monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in June 1995 (and for many years prior to June 1995) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target

and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identifying undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr. Leigh Anderson to found the Large Scale Biology Corporation in 1987, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pp. 1, 3, and 5).

Accordingly, the teachings in the Coleman '125 application, in particular regarding use of the SEQ ID NO:2 polypeptide in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies, and persons skilled in the art who read the Coleman '125 application on June 6, 1995 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), my experience with protein analysis methods in the mid-1980s and the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the June 6, 1995 filing date of the Coleman '125 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information. . . -- among others, . . . drug development and testing" (See Tab D, p. 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Coleman '125 application discloses that expression of TRH is associated with liver tissue and with the immune response (Coleman '125 application at page 7, lines 12-18; and page 22, lines 9-11). The Bjellqvist article showed that a

protein may be identified accurately by its positional coordinates, namely molecular mass and isoelectric point (See Tab F). The Coleman '125 application clearly disclosed SEQ ID NO:2 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on June 6, 1995 who read the Coleman '125 application, would understand that application to disclose the SEQ ID NO:2 polypeptide, and by extension the SEQ ID NO:2-encoding polynucleotides, to be highly useful in analysis of differential expression of proteins. For example, the specification of the Coleman '125 application would have led a person skilled in the art in June 1995, who was using protein expression monitoring in connection with developing new drugs for the treatment of immune disorders and trauma, to conclude that a 2-D PAGE map that used the isolated SEQ ID NO:2 polypeptide would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:2 polypeptide. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:2 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating immune disorders and trauma for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(c) below a number of reasons why a person skilled in the art, who read the Coleman '125 specification in June 1995, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:2 polypeptide would be a highly useful tool for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for immune disorders and trauma by means of 2-D PAGE maps, as well as for other evaluations.

(a) The Coleman '125 specification contains a number of teachings that would lead persons skilled in the art on June 6, 1995 to conclude that a 2-D PAGE map that utilized the

substantially purified SEQ ID NO:2 polypeptide would be a more useful tool for gene and protein expression monitoring applications relating to drugs for treating immune disorders and trauma than a 2-D PAGE map that did not use the SEQ ID NO:2 polypeptide. Among other things, the Coleman '125 specification teaches that (i) the identity of the SEQ ID NO:2 polypeptide was determined from "the cDNAs of a liver library," (ii) the SEQ ID NO:2 polypeptide is the thrombin receptor homolog referred to as TRH, and (iii) "[s]ince TRH was found in a human liver library, it appears to be upregulated in cell types mainly involved in immune protection or defense" (Coleman '125 application at page 5, lines 2-5; page 7, lines 12-18; and page 22, lines 9-11; see paragraph 9, *supra*). The substantially purified SEQ ID NO:2 polypeptide could, therefore, be used as a control to more accurately gauge the expression of TRH in a sample, and consequently more accurately gauge the effect of a toxicant on expression of the gene.

Moreover, the Coleman '125 specification teaches that the polypeptide encoded by SEQ ID NO:1 "is homologous to but significantly different from the GenBank sequence, HUMTHRR" (Coleman '125 application at page 7, lines 14-15; and Figures 2A, 2B, and 2C). HUMTHRR is the human thrombin receptor, a G-protein coupled seven transmembrane receptor (T7G) (Coleman '125 application at page 1, line 3; and page 2, lines 10-11). In addition, the SEQ ID NO:2 polypeptide "displays amino acid sequence similarity to platelet activating factor receptor (residues 94-155). These amino acids cover most of TMS III, the second intracellular loop, and TMS IV" (Coleman '125 application at page 2, lines 11-13; and Figures 2A, 2B, and 2C).

T7Gs (also known as GPCRs), such as thrombin receptor, are well known as intracellular signal mediators with diverse functions in complex organisms. T7Gs perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates. For example, the Stadel review lists examples of marketed drugs targeted to T7Gs (See Tab H at page 432). Even those T7Gs for which the specific ligand is not yet known are recognized in the art as highly valuable targets for novel drug discovery. As the Stadel review discloses, "[b]ecause of the proven link of [T7Gs] to a wide variety of diseases and the historical success of drugs that target [T7Gs], we believe that these orphan receptors are among the best

targets of the genomic era to advance into the drug discovery process" (See Tab H at page 436). Because of the relationship between TRH and T7Gs as a class, and because T7Gs are implicated in a wide variety of diseases and disorders, persons skilled in the art in June 1995 would have considered the SEQ ID NO:2 polypeptide, and by extension the SEQ ID NO:2-encoding polynucleotides, to be an important and valuable tool for analysis of a 2-D PAGE map for use in research on immune disorders and trauma.

(b) Also pertinent is that pre-June 1995 publications cited in the Coleman '125 specification or known in the art point to the potential role in specific disorders of previously known T7Gs having structural and chemical similarity to TRH. For example, the Wilcox article discloses that activation of thrombin receptor is associated with response to blood vessel injury. In particular, "upregulation of smooth muscle cell thrombin receptor expression occurs very early after vascular injury . . . the mitogenic effects of thrombin are receptor-mediated, and thrombin receptor expression is regulated by growth factors with established roles in vascular lesion formation" (See Tab I, e.g., the Abstract at page 1029).

(c) Persons skilled in the art on June 6, 1995 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized the SEQ ID NO:2 polypeptide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:2 polypeptide and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detract from my conclusion that persons skilled in the art on June 6, 1995, having read the Coleman '125 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating immune disorders and trauma (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:2 polypeptide. Persons skilled in the art on June 6, 1995 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:2 polypeptide because a 2-D PAGE map that utilized this polypeptide (as compared to one that did not) would provide more useful results in the kind of gene and protein expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to June 6, 1995.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Coleman '125 application disclosing to persons skilled in the art at the time of its filing specific, substantial, and credible real-world utilities for the SEQ ID NO:2 polypeptide, and by extension, the SEQ ID NO:2-encoding polynucleotides.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Coleman '125 disclosure regarding the uses of the SEQ ID NO:2 polypeptide for protein expression monitoring applications is <u>not</u> limited to the use of this protein in 2-D PAGE maps. For one thing, the Coleman '125 disclosure regarding techniques used in gene and protein expression monitoring applications is broad (Coleman '125 application at, e.g., page 6, lines 24-27; page 7, lines 18-25; page 8, lines 30-32; page 10, lines 11-19; page 22, lines 6-29; and page 26, line 33 to page 27, line 5).

In addition, the Coleman '125 specification repeatedly teaches that the protein described therein (including the SEQ ID NO:2 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

(a) Coleman '125 application at page 22, lines 7-18 ("Particular TRH antibodies are useful for investigating signal transduction and the diagnosis of infectious or hereditary conditions which are characterized by differences in the amount or distribution of TRH or downstream products of an active signalling cascade. . . Diagnostic tests for TRH include methods utilizing antibody and a label to detect TRH in human body fluids, membranes, cells, tissues or extracts of such. The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, the polypeptides and antibodies will be labeled by joining them, either covalently or noncovalently, with a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and have been reported extensively in both the scientific and patent literature"); and

(b) Coleman '125 application at page 22, lines 23-26 ("A variety of protocols for measuring soluble or membrane-bound TRH, using either polyclonal or monoclonal antibodies

specific for the protein, are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and fluorescent activated cell sorting (FACS)").

Thus, a person skilled in the art on June 6, 1995, who read the Coleman '125 specification, would have routinely and readily appreciated that the SEQ ID NO:2 polypeptide, disclosed therein, and by extension the SEQ ID NO:2-encoding polynucleotides, would be useful to conduct gene and protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Coleman '125 application. For example, a person skilled in the art in June 1995 would have routinely and readily appreciated that the SEQ ID NO:2 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of and immune disorders and trauma, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.

L. Michael Furness, B.Sc.

Signed at Mountain View, California
this 7th day of November, 2002.